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CASE REPORT

An OXA-48-producing *Escherichia coli* isolated from a Danish patient with no hospitalization abroad

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Abstract
Carbapenemase-producing organisms are disseminating globally and are now emerging as a worrying threat in Scandinavia. Before August 2013, OXA-48-producing organisms had not been detected in Danish patients. Here we report the isolation of an ST746 OXA-48-producing *Escherichia coli* with the plasmid pOXA-48a carrying the bla_{OXA-48} gene isolated from a Danish patient without history of hospitalization abroad. The patient reported tourist travel to Egypt and Turkey. The potential acquisition of carbapenemase-producing organisms by ingestion of contaminated food is discussed.

Keywords: *Travel-associated spread, OXA-48, carbapenem resistance, Enterobacteriaceae*

Introduction

Carbapenemase-producing organisms are disseminating globally and are now emerging as a worrying threat in Scandinavia. OXA-48 carbapenemase-producing *Enterobacteriaceae* were first detected in Istanbul in 2001 and have migrated from the Middle East and from North African countries to Europe [1,2]. OXA-48 producers can be difficult to detect due to low minimum inhibitory concentrations (MICs) to carbapenems and have gained a foothold in many European countries [1]. Before August 2013, OXA-48 producing organisms had not been detected from Danish patients. Here we report the finding of an ST746 OXA-48-producing *Escherichia coli* with the plasmid pOXA-48a carrying the bla_{OXA-48} gene from a Danish patient without history of hospitalization abroad.

Case report

The isolate was obtained from a 64-year-old female diagnosed with systemic sclerosis in 1989. Since May 2011, the patient had received erythromycin 250 mg twice daily, in combination with a proton pump inhibitor due to involvement of the gastrointestinal tract. She had not received immunosuppressive treatment. In February and June 2013, the patient was on holiday for a week in Egypt and Turkey, respectively. No episodes of diarrhea were reported. In June, upon return from Turkey, the patient consulted her general practitioner and was successfully treated for an uncomplicated urinary tract infection with pivmecillinam, 400 mg three times daily. Unfortunately, no urine was sent for culture before initiating treatment and urine culture after treatment was without growth. In August, 2 months after returning from Turkey, culture of urine after an annual follow-up for systemic sclerosis revealed an *E. coli* isolate resistant to amoxicillin-clavulanate (minimum inhibitory concentration (MIC) >16 mg/L) and piperacillin-tazobactam (MIC $= 32$ mg/L). The patient did not report symptoms of urinary tract infection.

Antimicrobial susceptibility testing was performed by broth microdilution (Sensititre; Trek Diagnostics System, East Grinstead, UK), except for the MICs of ertapenem and ciprofloxacin, which

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were determined by Etest (bioMérieux, Marcy-I'Étoile, France). Results were interpreted according to EUCAST guidelines (http://www.eucast.org).

The MIC of meropenem (MIC = 0.5 mg/L) was slightly above the EUCAST epidemiological cut-off, well within the susceptible range; however, the isolate was resistant to ertapenem (MIC = 8 mg/L). The isolate was susceptible to all cephalosporins tested and to ciprofloxacin (MIC = 0.032 mg/L). The MICs are shown in Table I. Consistent with previous findings [3], the isolate expressed high-level resistance to temocillin by disk diffusion and there was no observed synergy between meropenem/boronic acid or meropenem/dipicolinic acid.

The isolate was subjected to whole genome sequencing (WGS). Genomic DNA was extracted (DNeasy Blood and Tissue Kit, Qiagen, Copenhagen, Denmark) and fragment libraries were constructed using the Nextera Kit (Illumina, Little Chesterford, UK) followed by 250 bp paired end sequencing (MiSeq, Illumina) according to the manufacturer's instructions. Multilocus sequence typing (MLST) was performed using the MLST web server (www.genomicepidemiology.org) and the ResFinder web server (www.genomicepidemiology.org) was used to identify acquired antimicrobial resistance genes. WGS showed that the *E. coli* isolate belonged to sequence type ST746 and revealed that the isolate harbored bla_{OXA-48} and bla_{TEM-1} genes. The bla_{OXA-48} gene was carried on an IncL/M-type plasmid showing 100% homology to the sequence of plasmid pOXA-48a reported by Poirel et al. [4], consistent with reports suggesting that the spread of OXA-48 carbapenemase producers is mainly related to dissemination of this plasmid [1,2].

Table I. Minimum inhibitory concentrations (MICs) of antimicrobial agents.

Antimicrobial agent	MIC (mg/L)
Penicillins	
Ampicillin	>16
Amoxicillin/clavulanate	>16
Piperacillin/tazobactam	32
Cephalosporins	
Cefepime	<1
Cefotaxime	<0.25
Cefoxitin	4
Cefpodoxime	<0.25
Ceftazidime	<0.25
Ceftriaxone	<1
Carbapenems	
Ertapenem	8
Imipenem	0.25
Meropenem	0.5
Fluoroquinolones	
Ciprofloxacin	0.032
Aminoglycosides	
Gentamicin	>16

Discussion

The *E. coli* isolate belonged to sequence type ST746, a sequence type rarely detected in human clinical isolates. Published studies link this sequence type to wild birds and poultry [5–7]. As the patient had no healthcare-related exposure in the visited countries, it was suspected that the source of infection could be ingestion of contaminated food. Currently, there is no systematic testing for carbapenemase-producing bacteria in food, but detection of carbapenemases in food has been reported recently [8]. Several studies suggest a link between human clinical isolates producing extended-spectrum beta-lactamases (ESBLs) and ESBLs in poultry [9,10], but so far the possibility of a connection between carbapenemases in food and clinical carbapenemase-producing isolates has not been investigated.

Recent studies have demonstrated that international travel is a major risk factor for acquisition of ESBL-producing *Enterobacteriaceae*, with colonization rates up to 46% depending on the geographic area visited [11,12]. However, transmission of carbapenemase-producing *Enterobacteriaceae* has mainly been healthcare associated up till now and screening procedures have been restricted to patients transferred from hospitals abroad. In parallel to acquisition of ESBL-producing *Enterobacteriaceae*, this case and recent reports suggest that transmission of carbapenemase-producing *Enterobacteriaceae* now occurs in the community in endemic areas and indicate that tourist travel may constitute a risk of colonization with carbapenemase-producing *Enterobacteriaceae* [13,14].

Adequate screening and detection methods for carbapenemase producers, especially the OXA-48-type carbapenemases, are essential. OXA-48-producing *Enterobacteriaceae* are easily missed as they do not grow on selective media for detection of ESBL producers and may not be detected due to low carbapenem MICs. The *E. coli* isolate detected in this case was susceptible to cephalosporin and had a meropenem MIC well below the clinical breakpoint. Carbapenemase production was only suspected due to the use of the epidemiological cut-off for meropenem in our laboratory.

In conclusion, we report a case of acquisition of an OXA-48-producing *E. coli* after tourist travel to endemic areas without any contact with local healthcare providers. This case and recent reports of acquisition of carbapenemase producers by healthy travelers suggest that screening measures for international travelers may now be necessary to

prevent the spread of carbapenemase-producing *Enterobacteriaceae*.

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